22. (Amended) A pharmaceutical composition [selected from the group] comprising [consisting of tumor cells,] tumor cell extracts comprising a peptide[, and] or a mixture of tumor cells and tumor cell extracts comprising a peptide, said composition mixed with an immunological adjuvant, said composition useful for the treatment of [cancer] melanoma.

Claim 23, line 3, following "autologous" delete "," insert therefor --or--;

Claim 23, line 3, following "allogeneic", delete ", or stem cells".

REMARKS

Claims 1-7, 10-31 are pending in the above-identified application. Claims 11-21 are canceled above without prejudice to the filing of one or more divisional applications.

The disclosure is objected to in regard to the language "*Bacille*," "DFS," and "TS". Applicant encloses herewith the first pages of two references wherein "BCG" is identified as bacille Calmette-Guerin and Bacillus Calmette-Guerin, see Veronesi, *et al.*, *NEJM* **1982**, *307*:913 and Laucius, *et al.*, *Cancer* **1977**, *40*:2091, respectively. Nonetheless, the specification is amended above such that "*Bacille*" is replaced with *Bacillus*, DFS is replaced with disease-free survival (DFS) and "TS" is replaced with total survival (TS). Those of ordinary skill in the art would recognize the misspelling of "*Bacillus*," support for the

insertion of "disease-free survival" and "total survival" may be found in the specification as filed, in Example 6, page 41, lines 14-15.

The specification is objected to for not providing a graph which is referred to on page 24. The text objected to is deleted from the specification as set forth in the amendments to the specification above.

In view of the amendments to the specification and the remarks set forth above, Applicant respectfully requests withdrawal of the objection to the specification.

Claims 1-7, 10, and 22-31 are rejected under 35 U.S.C. §112, second paragraph as indefinite. In regard to claims 2 and 23 this rejection is due to the inclusion of the language "stem cells." It appears that this rejection is directed to claims 4, and 23, which are amended above to delete "stems cells."

Claim 1 is rejected as it is apparently unclear whether the hapten is conjugated to the irradiated composition or whether it is separately added to the composition. Claim 1 is amended above such that the hapten is conjugated to the irradiated composition.

Claims 1, 4, 22, 30, and 31 are indicated to be vague due to the language "tumor cell extracts." The language of independent claims 1 and 22 is amended such that tumor cell extracts comprise a peptide. Support for this language may be

found in the specification as filed as pointed out by the Examiner in the Office Action dated April 7, 1995. The peptide may be isolated from the cell surface of a cancerous cell. By definition recognized by those of skill in the art, peptide includes the definition of a protein, as peptides and proteins includes more than one amino acid linked by the carboxyl group of one amino acid to the amino group of another amino acid. Accordingly, the definitions set forth in the specification are consistent and not contradictory.

In view of the amendments to claims 1, 4, 22, and 23, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

Claims 22, 26, and 27 are rejected under 35 U.S.C. §112, fourth paragraph as improperly dependent on a previous claim. Claim 22 is amended above such that claims 26 and 27 are properly dependent therefrom. Accordingly, the rejection under 35 U.S.C. §112, fourth paragraph should be withdrawn.

The specification is objected to and claims 1-7, 10, and 22-31 are rejected under 35 U.S.C. §112, first paragraph as failing how to adequately make and use the invention. Applicant's direction is directed to the Rotzschke *et al.* reference which describes the isolation of viral peptides from major histocompatibility complex class I molecules in tumor cells infected with virus. While Applicant adapted the Rotzschke *et*

al. method of isolating peptides to the isolation of peptides of the present invention, the present invention is not directed to viral infection.

In regard to the references of Rotzschke *et al.*, Bystryn, Finn, Helstrom *et al.*, Livingston *et al.*, and Hoover *et al*. cited by the Examiner in the Office Action dated April 7, 1995, Applicant respectfully points out that these references, however, are taken out of context.

The references cited above do not provide the required burden for a showing of enablement as provided by the M.P.E.P., the Board of Patent Appeals and Interferences, and the Court of Appeals and Interferences. Applicant directs the Examiner's attention to *In re Jolles*, 206 U.S.P.Q. 885, 890 (C.C.P.A. 1980) where the Examiner and the solicitor were reprimanded by court for failing to support their assertion of "incredible utility." While the predictability of the similarity between the disclosures of the cited references and the present invention is apparent to the Examiner, at the same time, the unpredictability in the art and the claimed method results in rejections under §112.

Applicant has met the burden provided by M.P.E.P. §608.01(p), the Board of Patent Appeals and Interferences, and the Court of Appeals for the Federal Circuit in establishing the enablement and written description requirement of the present

invention. In view of the remarks set forth herein, Applicant has met the burden of proof required to establish enablement and written description of the present invention and the burden has now shifted to the Examiner. Accordingly, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

In view of the remarks set forth above and the amendments to claims 1 and 22 above such that the method and composition of the present invention are directed to melanoma, Applicant respectfully requests withdrawal of the objection to the specification and rejection of the claims.

Claims 1-6 and 22-29 are rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 1 and 2 of U.S. Patent No. 5,290,551. Claims 1 and 22 are amended above such that the language "tumor cells" is deleted therefrom. The 5,290,551 Patent does not claim tumor cell extracts comprising a peptide or a mixture of tumor cells and tumor cell extracts comprising a peptide. Further, there is no disclosure in the specification of 5,290,551 which suggests the tumor cells may be mixed with tumor cell extracts comprising a peptide. Thus, as the claims of the present application do not contain all of the limitations of claims 1 and 2 of U.S. Patent No. 5,290,551, claims 1-6 and 22-29 of the present invention are patentably distinct therefrom.

Accordingly, in view of the amendments to claims 1 and 22 and the remarks set forth above, Applicant respectfully requests withdrawal of the obviousness-type double patenting rejection.

Claims 1-6 and 22-29 are rejected under 35 U.S.C. §102(a) as anticipated by Murphy *et al*.

The standard for anticipation under §102 is one of strict identity. An anticipation rejection requires a showing that each limitation of a claim be found in a single reference, *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 224 USPQ 409, 411 (Fed. Cir. 1984).

The present invention is directed to a method for treating melanoma comprising administering to a patient a therapeutically effective amount of cyclophosphamide; administering a therapeutically effective amount of a composition comprising an irradiated composition of tumor cell extracts comprising a peptide or a mixture of tumor cells and tumor cell extracts comprising a peptide, wherein said tumor cell extracts comprising a peptide or said mixture of tumor cells and tumor cell extracts comprising a peptide is conjugated to a hapten (claim 1) and a pharmaceutical composition comprising tumor cell extracts comprising a peptide or a mixture of tumor cells and tumor cell extracts comprising a peptide, said composition mixed with an immunological adjuvant, said composition useful for the treatment of melanoma (claim 22).

The disclosure of Murphy *et al.* is directed to a method of treating melanoma comprising administering to a patient a therapeutically effective amount of autologous, irradiated DNP-conjugated melanoma cells mixed with BCG. This is not Applicant's invention. Murphy *et al.* do not disclose tumor cell extracts comprising a peptide or a mixture of tumor cells and tumor cell extracts comprising a peptide for use in treating melanoma. In view of the standard set forth by *Atlas Powder*, the amendments to the claims and the remarks set forth herein, it is respectfully requested that the rejection under 35 U.S.C. §102(a) be withdrawn.

Claims 1-7 and 22-29 are rejected under 35 U.S.C. §102(a) as anticipated by Berd *et al.*, *Proc. Am. Assoc. Cancer Res. Ann. Meet.* **1990** *30*:382.

The standard for anticipation under §102 is one of strict identity. An anticipation rejection requires a showing that each limitation of a claim be found in a single reference, *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 224 USPQ 409, 411 (Fed. Cir. 1984).

The present invention is directed to a method for treating melanoma comprising administering to a patient a therapeutically effective amount of cyclophosphamide; administering a therapeutically effective amount of a composition comprising an irradiated composition of tumor cell extracts

comprising a peptide or a mixture of tumor cells and tumor cell extracts comprising a peptide, wherein said tumor cell extracts comprising a peptide or said mixture of tumor cells and tumor cell extracts comprising a peptide is conjugated to a hapten (claim 1) and a pharmaceutical composition comprising tumor cell extracts comprising a peptide or a mixture of tumor cells and tumor cell extracts comprising a peptide, said composition mixed with an immunological adjuvant, said composition useful for the treatment of melanoma (claim 22).

The disclosure of Berd *et al.* is directed to a method of treating melanoma comprising administering to a patient a therapeutically effective amount of autologous, irradiated DNP-conjugated melanoma cells mixed with BCG. This is not Applicant's invention. Berd *et al.* do not disclose tumor cell extracts comprising a peptide or a mixture of tumor cells and tumor cell extracts comprising a peptide for use in treating melanoma. In view of the standard set forth by *Atlas Powder*, the amendments to the claims and the remarks set forth herein, it is respectfully requested that the rejection under 35 U.S.C. §102(a) be withdrawn.

Claims 22-25, 28, and 29 are rejected under 35 U.S.C. §102(b) as anticipated by Berd *et al.*, *Cancer Res.* **1986** *46*:2572-2577 (reference AD of Applicant's Form 1449 submitted July 12, 1994).

The standard for anticipation under §102 is one of strict identity. An anticipation rejection requires a showing that each limitation of a claim be found in a single reference, *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 224 USPQ 409, 411 (Fed. Cir. 1984).

The present invention is directed to a method for treating melanoma comprising administering to a patient a therapeutically effective amount of cyclophosphamide; administering a therapeutically effective amount of a composition comprising an irradiated composition of tumor cell extracts comprising a peptide or a mixture of tumor cells and tumor cell extracts comprising a peptide, wherein said tumor cell extracts comprising a peptide or said mixture of tumor cells and tumor cell extracts comprising a peptide is conjugated to a hapten (claim 1) and a pharmaceutical composition comprising tumor cell extracts comprising a peptide or a mixture of tumor cells and tumor cell extracts comprising a peptide, said composition mixed with an immunological adjuvant, said composition useful for the treatment of melanoma (claim 22).

The disclosure of Berd *et al.* is directed to a method of treating melanoma comprising administering to a patient a therapeutically effective amount of autologous melanoma cells mixed with BCG. This is not Applicant's invention. Berd *et al.* do not disclose tumor cell extracts comprising a peptide or a

mixture of tumor cells and tumor cell extracts comprising a peptide for use in treating melanoma. In view of the standard set forth by *Atlas Powder*, the amendments to the claims and the remarks set forth herein, it is respectfully requested that the rejection under 35 U.S.C. §102(b) be withdrawn.

Claims 22-24, 28, and 30 are rejected under 35 U.S.C. §102(b) as anticipated by Pattillo.

The standard for anticipation under §102 is one of strict identity. An anticipation rejection requires a showing that each limitation of a claim be found in a single reference, *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 224 USPQ 409, 411 (Fed. Cir. 1984).

The present invention is directed to a method for treating melanoma comprising administering to a patient a therapeutically effective amount of cyclophosphamide; administering a therapeutically effective amount of a composition comprising an irradiated composition of tumor cell extracts comprising a peptide or a mixture of tumor cells and tumor cell extracts comprising a peptide, wherein said tumor cell extracts comprising a peptide or said mixture of tumor cells and tumor cell extracts comprising a peptide is conjugated to a hapten (claim 1) and a pharmaceutical composition comprising tumor cell extracts comprising a peptide or a mixture of tumor cells and tumor cell extracts comprising a peptide, said composition mixed

with an immunological adjuvant, said composition useful for the treatment of melanoma (claim 22).

The disclosure of Pattillo is directed to a method of treating malignancies of the reproductive tract, see page 809, "Materials and methods." The Pattillo method comprises administering to a patient BCG. Tumor antigen is prepared and a filtrate is added to BCG and spread on the skin. This is not Applicant's invention. Pattillo does not disclose tumor cell extracts comprising a peptide or a mixture of tumor cells and tumor cell extracts comprising a peptide for use in treating melanoma. In view of the standard set forth by *Atlas Powder*, the amendments to the claims and the remarks set forth herein, it is respectfully requested that the rejection under 35 U.S.C. §102(b) be withdrawn.

Claims 1 and 10 are rejected under 35 U.S.C. §103 as unpatentable over Berd *et al.*, *Proc. Am. Assoc. Cancer Res. Ann. Meet.* **1990** *30*:382, or Murphy *et al.* in view of Geczy *et al.*

The present invention is directed to a method for treating melanoma comprising administering to a patient a therapeutically effective amount of cyclophosphamide; administering a therapeutically effective amount of a composition comprising an irradiated composition of tumor cell extracts comprising a peptide or a mixture of tumor cells and tumor cell extracts comprising a peptide, wherein said tumor cell extracts

comprising a peptide or said mixture of tumor cells and tumor cell extracts comprising a peptide is conjugated to a hapten (claim 1) and the method further comprising sensitizing the patient with a therapeutically effective amount of 1-fluoro-2,4-dinitrobenzene prior to administering cyclophosphamide (claim 10).

Berd *et al.* and Murphy *et al.* disclose a method of treating melanoma comprising administering whole cells mixed with BCG. Neither Berd *et al.* nor Murphy *et al.* disclose the administration of tumor cell extracts comprising a peptide or a mixture of tumor cells and tumor cell extracts comprising a peptide in the treatment of melanoma. Further, claim 1 does not require sensitization of the patient with DNFB prior to cyclophosphamide administration. Claim 10 is directed to the administration of DNFB prior to cyclophosphamide.

Berd *et al.* disclose the administration of DNCB and cyclophosphamide prior to administration of a vaccine comprising melanoma cells. Murphy *et al.* disclose administration of DNP and cyclphosphamide prior to administration of a vaccine comprising melanoma cells. Geczy *et al.* disclose that DNCB and DNFB may be used to elicit delayed hypersensitivity. However, there is no suggestion to combine the teachings of Berd *et al.* or Murphy *et al.* with the teachings of Geczy *et al.*

> Under section 103, teachings of references can be combined *only* if there is some

> suggestion or incentive to do so. . . The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification.

In re Fritsch, 23 USPQ2d 1780, 1783-1784 (Fed. Cir. 1992). Berd *et al.* or Murphy *et al.* do not suggest that DNCB or DNP may be replaced with DNCB or DNFB of Geczy *et al.* Further, lacking from any of the references is a teaching that sensitization of the patient to DNP is not needed in accordance with claim 1.

In view of the remarks set forth herein and the amendments to the claims above, Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. §103.

Claims 1-7, 10, and 22-29 are rejected under 35 U.S.C. §103 as unpatentable over Berd *et al.*, *Proc. Am. Assoc. Cancer Res. Ann. Meet.* **1990** *30*:382, in view of Fujiwara *et al.*,*J. Immunol.* **1980** *124*:863 (AQ of Applicant's Form 1449 submitted July 12, 1994) and Fujiwara *et al.*, *J. Immunol* **1984** *133*:510 (AS of Applicant's Form 1449 submitted July 12, 1994) and Geczy *et al.*

The remarks set forth above in regard to the teachings of Berd *et al.* and Geczy *et al.* are incorporated herein for the sake of brevity.

Fujiwara *et al.* (AQ) and (AS) teach away from the present invention as set forth by the following examples which distinguish Fujiwara *et al.* (AQ) and (AS) from the present

invention. Fujiwara *et al.* teach induced transplantable murine tumors and immunoprophylaxis.

Fujiwara et al. disclose a transplantable mouse tumor which is induced in one mouse; extracts of that tumor are then injected into other mice. On the other hand, human tumors treated with the vaccine of the present invention are spontaneous. Those of skill in the art understand that induced tumors are easier to manipulate than spontaneous tumors. In addition, results obtained with induced tumors are not applicable to treatments for spontaneous tumors. Furthermore, Fujiwara et al. employ the process of immunoprophylaxis. In this process, a normal mouse is treated with a vaccine. Several weeks later, that mouse is injected with live tumor cells. The investigator measures the growth of the tumor and compares it with the growth rate of the same tumor injected into another mouse of the same strain that had not received the vaccine. The DNP vaccine of the present invention is used in immunotherapy, in which a patient presents with a growing tumor. Only then is the patient treated with a vaccine. While immunoprophylaxis is more effective than immunotherapy, it is only possible to do immunotherapy in humans.

Further, it is noted that "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 USPQ2d 1780,

1784 (Fed. Cir. 1992). Under this standard, none of the prior art of record, alone or in any proper combination, discloses or suggests the present invention as defined by the amended claims. This is not to say that it is impossible to combine selected elements of several references to show the obviousness of an invention, however, there still must be a "suggestion or motivation in the prior art to make the selection." *In re Gorman*, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991) (claim held obvious in view of combined teachings of references showing elements for same purpose as claimed invention).

Accordingly, as Berd *et al.*, in view of Fujiwara *et al.* (AQ) and Fujiwara *et al.* (AS) and Geczy *et al.*, alone or in combination do not teach the present invention, the rejection under 35 U.S.C. §103 should be withdrawn.

In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration and allowance of all pending claims. Early and favorable notification to that effect is earnestly solicited.

Respectfully submitted,

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A RANDOMIZED TRIAL OF ADJUVANT CHEMOTHERAPY AND IMMUNOTHERAPY IN CUTANEOUS MELANOMA

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Abstract In a randomized trial of adjuvant chemotherapy, immunotherapy, or immunochemotherapy, 761 evaluable patients with pathological Stage II cutaneous melanoma anywhere on the body or with pathological Stage I melanoma of the trunk (Clark's level 3 to 5) were studied by the World Health Organization International Melanoma Group. Wide local excision and excisional regional lymphadenectomy alone were performed in 185 patients and the results were compared with those of surgery plus chemotherapy with dacarbazine (in 192 patients), surgery plus immunotherapy with bacille Calmette–Guérin vaccine (in 203), and surgery plus chemotherapy combined with immunotherapy (in 181).

The rates of disease-free survival and overall survival at 36 months were 30.4±6.3 per cent (mean ±S.E.) and 41.6±10.0 per cent, respectively, after surgical treatment alone; 37.2±7.9 per cent and 46.5±8.3 per cent after surgery plus chemotherapy; 34.8±7.9 per cent and 48.7±8.7 per cent after surgery plus immunotherapy; and 33.6±7.9 per cent and 50.0±8.8 per cent after surgery plus a combination of chemotherapy and immunotherapy. None of the differences between groups was significant, and thus no effect of adjuvant therapy could be demonstrated in this study. (N Engl J Med. 1982; 307:913-6.)

THE rationale for combining surgery and chemotherapy in the treatment of melanoma was developed from new concepts derived from studies in animals, which showed that the efficacy of chemotherapy is inversely related to the total tumor-cell burden. Chemotherapy was therefore considered more effective when given immediately after surgery rather than at the time of the appearance of clinical metastases.[1,2] In experimental models bacille Calmette-Guérin (BCG) vaccine was also useful as adjuvant therapy, in that it prevented the growth of tumor cells, reduced the volume of metastatic spread, and prolonged survival when given immediately after surgery.[3-5]

Although the first clinical trials suggested improvement in both disease-free and overall survival rates when radical surgery was combined with postoperative BCG,[6-8] opinions on the efficacy of adjuvant chemotherapy or immunotherapy in human beings now vary. Some investigators[6-9] have confirmed the benefit of surgery followed by adjuvant treatment in cutaneous melanoma; others[10-12] have reported no effect. The diversity of opinions is mainly due to a lack of data from well-conducted clinical trials, to different treatment schedules,[7,13] to the small number of patients studied,[8,10,11,14,15] and to short follow-up periods. We now report the results of a prospective randomized clinical trial carried out by the World Health Organization International Melanoma Group to compare the effects of adjuvant therapy with 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide (dacarbazine), BCG, or both after conventional surgical treatment.

Methods

From June 1974 to October 1980, 931 high-risk patients entered the study after a "radical" surgical procedure had been performed. Twenty centers took part in the study. All patients with melanoma who were thought to be at high risk of recurrence were considered; such patients had histologically proved lymph-node metastases (pathological stage II) or Clark's level 3 to 5 melanoma of the trunk with histologically uninvolved regional nodes (pathological Stage I). These two groups of patients were randomized separately. Of the 761 evaluable patients, 663 were in histologic Stage II and 98 were in pathological Stage I.

Surgical Treatment

The primary melanoma was excised with borders at 3 to 5 cm of normal skin and to a depth including the fascia of the underlying muscle. All patients had a "radical" lymph-node dissection. Patients with no palpable node entered the study provided that lymphatic drainage was to a single lymph-node-bearing area. The following node dissections were considered adequate: radical neck dissection, radical axillary dissection up to the subclavian muscle with en bloc removal of pectoralis minor muscle, and radical inguinal and iliac lymphadenectomy including the inguinocrural, external iliac, and obturator-node groups.

Adjuvant Treatment

Adjuvant chemotherapy treatment was begun 10 to 20 days after surgery. The initial dose of intravenous dacarbazine was 200 mg per square meter of body-surface area, given daily for five consecutive days. The cycles were repeated every fours weeks for 24 cycles if there was no evidence of recurrent disease.

For adjuvant immunostimulation, lyophilized BCG, 75 mg (Institut Pasteur), was administered with "Heaf gun" needles at the 2-mm setting. Lyophilized BCG was reconstituted in a 0.5-ml saline

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The following institutions participated in this trial: Abteilung für Klinische Immunologie, Medizinische Hochschule, Hanover, Federal Republic of Germany; Abteilung für Klinische und Experimentelle Dermatologie, Giessen, Federal Republic of Germany; Centro Medico Oncologico, Ospedali Riuniti, Parma, Italy; Fondation Curie, Paris; Het Nederlands Kankerinstituut, Amsterdam; Hospital de Clinicas "M. Quintela," Montevideo, Uruguay; Institute of Oncology, Belgrade; Yugoslavia; Institut Jules Bordet, Brussels; Instituto Nacional de Cancer, Rio de Janeiro; Institute J. Paoli Calmettes, Marseilles; Istituto di Oncologia, Genoa; Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan; Oncological Institute, Brno, Czechoslovakia; Oncological Institute, Gliwice, Poland; Oncological Research Institute, Sofia, Bulgaria; Oncological Institute, Warsaw; Rotterdamsch Radiotherapeutisch Instituut, Rotterdam; Sydney Hospital, Sydney, Australia; State Institute of Oncology, Budapest; and the University of Glasgow, Department of Dermatology, Glasgow, Scotland.

A PHASE II STUDY OF AUTOLOGOUS IRRADIATED TUMOR CELLS PLUS BCG IN PATIENTS WITH METASTATIC MALIGNANT MELANOMA

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Eighteen patients with surgically incurable metastatic malignant melanoma were treated with a mixture of irradiated (15,000 rads) autologous tumor cells ($1–2 \times 10^8$) and BCG (Glaxo, $2–4.5 \times 10^8$ organisms), which was injected intradermally (in five divided doses) every 2 weeks (×5). Four of 18 (22%) evaluable patients achieved objective remissions. It is concluded that this treatment regimen does not have general clinical application because the remissions were infrequent, of short duration (median, 3 months) and occurred only in patients with minimal, nonvisceral tumor burdens.

Cancer 40:2091–2093, 1977.

IMMUNIZATION WITH TUMOR CELLS OR CELL fractions is effective in animal systems in inducing resistance to subsequent tumor transplants. However, such procedures are largely ineffective in inducing regression of established tumors. Similarly, attempts to immunize tumor-bearing melanoma patients with irradiated autologous tumor cells have shown no therapeutic benefit. Of 39 patients treated, only one objective response was noted.[2,4,5] The failure to achieve successful therapy by active specific immunization with tumor cells may be related in part to the low degree of immunogenicity of the immunizing material. One approach to enhancing the immunogenicity of tumor cells is to admix them with an adjuvant such as Bacillus Calmette-Guerin (BCG). Our experience with intralesional BCG in patients with dermal melanoma metastases reinforced this concept.[7,8] Of particular interest was the apparent regression of uninjected nonregional lymph node metastases[8] and a pulmonary metastasis.[6] To test the therapeutic efficacy of one such combination, a Phase II trial of irradiated autologous tumor cells admixed with BCG was initiated in patients with metastatic malignant melanoma.

MATERIALS AND METHODS

The criteria for entrance to this study were: 1) histologically documented, surgically incurable, measurable, metastatic malignant melanoma; 2) tumor accessible for vaccine preparation; 3) a life expectancy in excess of 2 months; 4) white blood cell count in excess of 4000/mm^3; 5) platelet count in excess of 100,000/mm^3; 6) total serum bilirubin less than 2 mg/100 ml; 7) SGOT less than 50 units; and 8) no chemotherapy within the preceding 28 days. Patients were excluded who had brain metastases or who were receiving steroid therapy.

Prior to the initiation of therapy, patients were evaluated to determine the extent and distribution of their metastatic disease. This evaluation included a history and physical examination, complete blood and platelet counts, BUN, liver function profile (total serum bilirubin, SGOT, LDH, alkaline phosphatase), chest x-ray, and liver, brain and bone scans. Complete blood and platelet counts were repeated every 2 weeks. The chest x-ray, BUN, and liver function profile were repeated at 8-week intervals; liver, brain and bone scans were repeated when clinically indicated.

Before treatment, the immunologic status of each patient was evaluated by quantitation of immunoglobulins, serum hemolytic complement

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